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PATENT COOPERATION TREATY

PCT

09/485071 4

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

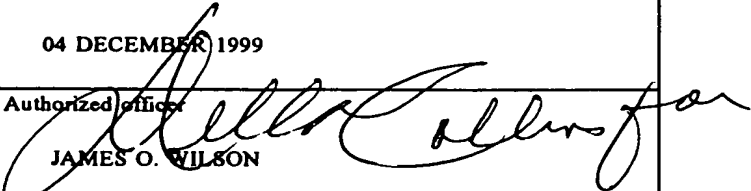
Applicant's or agent's file reference 30794.30WO0		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US98/12351	International filing date (day/month/year) 12 JUNE 1998	Priority date (day/month/year) 29 AUGUST 1997	
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.			
Applicant THE REGENTS OF THE UNIVERSITY OF CALIFORNIA			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets.
☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 29 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 12 MARCH 1999	Date of completion of this report 04 DECEMBER 1999
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer  JAMES O. WILSON
Facsimile No. (703) 305-3230	Telephone No. (703) 308-1235

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US98/12351

I. Basis of the report

1. This report has been drawn on the basis of *(Substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments)*:

- ☐ the international application as originally filed.
- ☒ the description, pages (See Attached) , as originally filed.
pages _____ , filed with the demand.
pages _____ , filed with the letter of _____
pages _____ , filed with the letter of _____
- ☒ the claims, Nos. (See Attached) , as originally filed.
Nos. _____ , as amended under Article 19.
Nos. _____ , filed with the demand.
Nos. _____ , filed with the letter of _____
Nos. _____ , filed with the letter of _____
- ☒ the drawings, sheets/fig (See Attached) , as originally filed.
sheets/fig _____ , filed with the demand.
sheets/fig _____ , filed with the letter of _____
sheets/fig _____ , filed with the letter of _____

2. The amendments have resulted in the cancellation of:

- ☒ the description, pages NONE
- ☒ the claims, Nos. NONE
- ☒ the drawings, sheets/fig NONE

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the ~~Supplemental Box~~ Additional observations below (Rule 70.2(c)).

4. Additional observations, if necessary:

NONE

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US98/12351III. **Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The question whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application.

☒ claims Nos. 14 and 22

because:

☐ the said international application, or the said claim Nos. _ relate to the following subject matter which does not require international preliminary examination (*specify*).

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 14 and 22 are so unclear that no meaningful opinion could be formed (*specify*).

Claims 14 and 22 depend from claim 11 and any one of claims 1-10 and claim 12 and any one of claim 1-10, respectively. Although the reference to claims 1-10 is alternative in each claim, the claims are not alternatively dependent from claims 11 or 12, as well as any one of claims 1-10. Any dependent claim which refers to more than one other claim shall refer to such claims in the alternative only. The reference to claims 11 and anyone of 1-10 in claim 14 and claim 12 and any one of claims 1-10 is not alternative. Each of claims 14 and 22 is improperly multiply dependent.

☐ the claims, or said claims Nos. _ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US98/12351

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. STATEMENT**

Novelty (N)

Claims 1-13, 15-21 and 23-25

YES

Claims NONE

NO

Inventive Step (IS)

Claims 1-13, 15-21 and 23-25

YES

Claims NONE

NO

Industrial Applicability (IA)

Claims 1-13, 15-21 and 23-25

YES

Claims NONE

NO

2. CITATIONS AND EXPLANATIONS

Claims 1-13, 15-21 and 23-25 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest the incorporation of the specific monomeric nucleoside moiety, which is C-5-methylcytosine. The prior art does not teach or fairly suggest a process for the inhibition of methylation of DNA using a compound which is an oligonucleotide containing a C-5-methylcytosine, nor does the prior art teach or fairly suggest a method for the inhibition of cancer cells or a method for identifying a molecule which binds to an allosteric site on the enzyme DCMTase.

NEW CITATIONS

NONE

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US98/12351

Suppl mental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: B xes I - VIII

Sheet 10

CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below:

IPC(6): G01N 31/00 and US Cl.: 435/6

514/43

536/22.1, 23.1, 23.2, 25.32

I. BASIS OF REPORT:

This report has been drawn on the basis of the description,
pages, 1-81, as originally filed.

pages, NONE, filed with the demand.

and additional amendments:

NONE

This report has been drawn on the basis of the claims,
numbers, NONE, as originally filed.

numbers, NONE, as amended under Article 19.

numbers, NONE, filed with the demand.

and additional amendments:

Claims 1-25, filed with the letter of 14 October 1999.

This report has been drawn on the basis of the drawings,
sheets, NONE, as originally filed.

sheets, NONE, filed with the demand.

and additional amendments:

Sheets 1-26, filed with the letter of 14 October 1999.

PATENT COOPERATION TREATY

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PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

CANADY, Karen, S.
Gates & Cooper
Suite 1050
6701 Center Drive West
Los Angeles, CA 90045
ÉTATS-UNIS D'AMÉRIQUE

Date of mailing (day/month/year) 22 April 1999 (22.04.99)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference 30794-30WO1	
International application No. PCT/US98/12351	International filing date (day/month/year) 12 June 1998 (12.06.98)

1. The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☒ the agent ☐ the common representative

Name and Address

CANADY, Karen, S.
Merchant, Gould, Smith, Edell,
Welter & Schmidt
Suite 400
11150 Santa Monica Boulevard
Los Angeles, CA 90025-3395
United States of America

State of Nationality

State of Residence

Telephone No.

310 445 1140

Facsimile No.

310 445 9031

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address

CANADY, Karen, S.
Gates & Cooper
Suite 1050
6701 Center Drive West
Los Angeles, CA 90045
United States of America

State of Nationality

State of Residence

Telephone No.

310 641 8797

Facsimile No.

310 641 8798

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office ☐ the designated Offices concerned
☐ the International Searching Authority ☒ the elected Offices concerned
☒ the International Preliminary Examining Authority ☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Nicola Wolff

Telephone No.: (41-22) 338.83.38



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TX 31651 epo nl
FAX +31 70 340 3016

Europäisches
Patentamt

Zweigstelle
in Den Haag
Recherchen-
abteilung

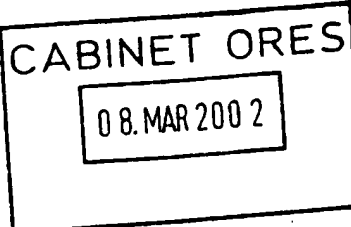
European
Patent Office

Branch at
The Hague
Search
division

Office européen
des brevets

Département à
La Haye
Division de la
recherche

Vialle-Presles, Marie José
Cabinet Orès,
6, Avenue de Messine
75008 Paris
FRANCE



Datum/Date
07.03.02

Zeichen/Ref./Réf. MJPcfC1403/1EPO	Anmeldung Nr./Application No./Demande n°/Patent Nr./Patent No./Brevet n°. 98930207.0-1521-US9812351
Anmelder/Applicant/Demandeur/Patentinhaber/Proprietor/Titulaire The Regents of the University of California	

COMMUNICATION

The European Patent Office herewith transmits as an enclosure the European search report for the above-mentioned European patent application.

If applicable, copies of the documents cited in the European search report are attached.

☐ Additional set(s) of copies of the documents cited in the European search report is (are) enclosed as well.

REFUND OF THE SEARCH FEE

If applicable under Article 10 Rules relating to fees, a separate communication from the Receiving Section on the refund of the search fee will be sent later.





European Patent
Office

**SUPPLEMENTARY
PARTIAL EUROPEAN SEARCH REPORT**

Application Number

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

EP 98 93 0207

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
① X	EP 0 756 008 A (HEALTH RESEARCH INC ;CHRISTMAN JUDITH K (US); SHEIKHNEJAD GHOLAMRE) 29 January 1997 (1997-01-29) * page 3, line 25-44 * * page 6, line 42 - page 7, line 1 * * table 9 * * claims 1,3,5,11 * Y * page 5, line 44-46 *	1,2,4-9, 11-17 10-17	G01N31/00 C12N9/10
② X	FLYNN JAMES ET AL: "Murine DNA cytosine-C-5 methyltransferase: Pre-steady- and steady-state kinetic analysis with regulatory DNA sequences." BIOCHEMISTRY, vol. 35, no. 23, 1996, pages 7308-7315, XP002189815 ISSN: 0006-2960 Y * tables 1,3 *	1,2,4-10 10-17	
			TECHNICAL FIELDS SEARCHED (Int.Cl.6)
			C12N A61K G01N

The supplementary search report has been based on the last set of claims valid and available at the start of the search.

INCOMPLETE SEARCH

The Search Division considers that the present application, or some or all of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for the following claims:

Claims searched completely :

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

see sheet C

4

EPO FORM 1503 03.82 (P04C20)

Place of search BERLIN	Date of completion of the search 18 February 2002	Examiner ALCONADA RODRIG., A
CATEGORY OF CITED DOCUMENTS		
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		
T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document		



DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
③ X	TOLLEFSBOL TRYGVE O ET AL: "Control of methylation spreading in synthetic DNA sequences by the murine DNA methyltransferase." JOURNAL OF MOLECULAR BIOLOGY, vol. 269, no. 4, 20 June 1997 (1997-06-20), pages 494-504, XP002189816 ISSN: 0022-2836 * page 497, right-hand column, last paragraph - page 499, right-hand column, last paragraph; table 1 * ----	1,2,4-9	
④ A	US 5 578 716 A (SZYF MOSHE ET AL) 26 November 1996 (1996-11-26) * the whole document * ----	1,2,4-20	TECHNICAL FIELDS SEARCHED (Int.Cl.6)
⑤ P,X	WO 97 44346 A (UNIV MCGILL ;SZYF MOSHE (CA); BIGEY PASCAL (FR)) 27 November 1997 (1997-11-27) * page 19, line 30 - page 20, line 22 * * page 20, line 28 - page 22, line 12 * * example 7; table I * See inhibitors of SEQ ID NO:13,15, 20 and 25. ----	1,2,4-9, 11-20	
⑥ P,X	FLYNN JAMES ET AL: "DNA binding discrimination of the murine DNA cytosine-C5 methyltransferase." JOURNAL OF MOLECULAR BIOLOGY, vol. 279, no. 1, 29 May 1998 (1998-05-29), pages 101-116, XP002189817 ISSN: 0022-2836 * the whole document * -----	1,2,4-20	



Claim(s) searched completely:
10 and 18-20

Claim(s) searched incompletely:
1, 2, 4-9 and 11-17

Claim(s) not searched:
3

Reason for the limitation of the search:

Present claims 1-9 and 11-17 relate to synthetic oligonucleotides comprising C-5 methylcytosine defined by reference to a desirable characteristic or property, namely, that they recognize and bind an allosteric site on DNA cytosine methyltransferase (DCMTase) thereby modulating DCMTase activity, either by inhibition (claims 1,2,4-9 and 11-17) or by activation (claim 3). The claims cover all oligonucleotides having this characteristic or property, whereas the application provides support within the meaning of Article 84 EPC and disclosure within the meaning of Article 83 EPC for only a very limited number of such inhibitory oligonucleotides and for none of the stimulatory oligonucleotides. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 84 EPC). An attempt is made to define the oligonucleotides by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of claims 1, 2, 4-9 and 11-17 which appear to be clear, supported and disclosed, namely those parts relating to the oligonucleotides as shown in Figure 1B and designated GC-box bMET (SEQ ID NO:10), GC-box pMET (SEQ ID NO:10), GC-box cMET (SEQ ID NO:13), GC-box dMET (SEQ ID NO:14), GC-box eMET (SEQ ID NO:15), or CRE aMET (SEQ ID NO:11) and it has not been carried out for claim 3, since this claim lacks support or disclosure within the description.

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO.

EP 98 93 0207

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

18-02-2002

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0756008	A	29-01-1997	US 5652105 A	29-07-1997
			CA 2180505 A1	29-01-1997
			EP 0756008 A2	29-01-1997
			JP 9173099 A	08-07-1997
US 5578716	A	26-11-1996	AU 700264 B2	24-12-1998
			AU 1296195 A	19-06-1995
			CA 2177732 A1	08-06-1995
			EP 0731835 A1	18-09-1996
			JP 9511125 T	11-11-1997
			WO 9515378 A1	08-06-1995
			US 6054439 A	25-04-2000
			US 5919772 A	06-07-1999
WO 9744346	A	27-11-1997	AU 3355297 A	09-12-1997
			DE 69708878 D1	17-01-2002
			EP 0914324 A2	12-05-1999
			WO 9744346 A2	27-11-1997
			US 6268137 B1	31-07-2001
			US 2001041337 A1	15-11-2001

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : G01N 31/00	A1	(11) International Publication Number: WO 99/12027 (43) International Publication Date: 11 March 1999 (11.03.99)
(21) International Application Number: PCT/US98/12351 (22) International Filing Date: 12 June 1998 (12.06.98) (30) Priority Data: 60/057,411 29 August 1997 (29.08.97) US (71) Applicant (for all designated States except US): THE REGENTS OF THE UNIVERSITY OF CALIFORNIA [US/US]; Fifth floor, 1111 Franklin Street, Oakland, CA 94607-5200 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): REICH, Norbert, O. [US/US]; 450 San Domingo Drive, Santa Barbara, CA 93111 (US). FLYNN, James [US/US]; 5658 Armitos Avenue, Goleta, CA 93117 (US). (74) Agent: CANADY, Karen, S.; Merchant, Gould, Smith, Edell, Welter & Schmidt, Suite 400, 11150 Santa Monica Boulevard, Los Angeles, CA 90025-3395 (US).		(81) Designated States: CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(54) Title: MODULATORS OF DNA CYTOSINE-5 METHYLTRANSFERASE AND METHODS FOR USE THEREOF (57) Abstract A synthetic oligonucleotide comprising a C-5 methylcytosine and which recognizes and binds an allosteric site on DNA methyltransferase thereby inhibiting DNA methyltransferase activity is disclosed. Also disclosed is a composition comprising a synthetic oligonucleotide of the invention. The composition is useful for inhibiting DNA methyltransferase activity, thereby inhibiting the methylation of DNA. The composition can be a pharmaceutical composition useful for treating disorders associated with methylation defects, such as cancer and certain developmental disorders. Also disclosed is a method of inhibiting methylation of DNA. The method involves contacting a DCMTase with a synthetic oligonucleotide of the invention in the presence of the DNA, thereby resulting in an enzyme/synthetic oligonucleotide complex. The presence of the complex prevents catalysis, thereby inhibiting DNA methyltransferase activity. Also disclosed is a method of treating a disorder of cell proliferation or development by administering to a subject a synthetic oligonucleotide of the invention. The inhibition of DNA methyltransferase prevents the methylation of DNA thereby treating the disorder of cell proliferation or development.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
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AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Larvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
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DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/12351

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :G01N 31/00

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONEElectronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,578,716 A (SZYF et al) 26 November 1996, column 2, line 43 through column 8.	1-13,18-20



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*&* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

03 AUGUST 1998

Date of mailing of the international search report

24 SEP 1998

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

JAMES O. WILSON

Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/12351

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 14-17
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/12351

A. CLASSIFICATION OF SUBJECT MATTER:

US CL : 435/6; 514/43; 536/22.1, 23.1, 23.2, 25.32

B. FIELDS SEARCHED

Minimum documentation searched

Classification System: U.S.

435/6; 514/43; 536/22.1, 23.1, 23.2, 25.32

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

USPATFULL

WPIDS

CAS ONLINE

BIOSIS

What is claimed is:

1. A synthetic oligonucleotide comprising a C-5 methylcytosine and which recognizes and binds an allosteric site on DNA cytosine methyltransferase (DCMTase) thereby modulating DCMTase activity associated with the allosteric site.
2. The synthetic oligonucleotide of claim 1, wherein the modulating comprises inhibition.
3. The synthetic oligonucleotide of claim 1, wherein the modulating comprises activation.
4. The synthetic oligonucleotide of claim 1, wherein the C-5 methylcytosine is present as a 5mCpG dinucleotide.
5. The synthetic oligonucleotide of claim 1, wherein the DCMTase is from a mammal, bird, fish, amphibian, reptile, insect, plant or fungus.
6. The synthetic oligonucleotide of claim 5, wherein the mammal is selected from the group consisting of mouse and human.
7. The synthetic oligonucleotide of claim 1 having an inhibition constant of not greater than 1000 nM.
8. The synthetic oligonucleotide of claim 7 having an inhibition constant of not greater than 200 nM.
9. The synthetic oligonucleotide of claim 8 having an inhibition constant of not greater than 20 nM.
10. The synthetic oligonucleotide of claim 1 comprising a nucleotide sequence as shown in Figure 1B and designated GC-box b^{MET} (SEQ ID NO:10), GC-box p^{MET} (SEQ ID NO:10), GC-box c^{MET} (SEQ ID NO:13), GC-box d^{MET} (SEQ ID NO:14), GC-box e^{MET} (SEQ ID NO:15), or CRE a^{MET} (SEQ ID NO:11).
11. A method of inhibiting methylation of DNA comprising contacting a DCMTase with a synthetic inhibitor molecule so as to form an enzyme/synthetic inhibitor molecule complex in the presence of the DNA, wherein the synthetic inhibitor

molecule comprises a C-5 methylcytosine which recognizes and binds an allosteric site on DCMTase, thereby inhibiting DNA methyltransferase activity.

12. A method of inhibiting proliferation of cancer cells comprising administering to a subject a synthetic inhibitor molecule which recognizes and binds an allosteric site on DCMTase thereby resulting in an enzyme/synthetic inhibitor molecule complex, the presence of the complex inhibiting DCMTase-mediated methylation of DNA, thereby inhibiting proliferation of the cancer cells.
13. The method of claim 12, wherein the cancer cell is from lung, breast, prostate, pancreas or colon.
14. The method of claim 11 or 12, wherein the synthetic inhibitor molecule is an oligonucleotide of any one of claims 1-10.
15. The method of claim 12, 13, or 14, wherein the subject is a human.
16. The method of claim 12, 13, or 14, wherein the subject is an animal.
17. The method of claim 16, wherein the animal is porcine, piscine, avian, feline, equine, bovine, ovine, caprine or canine.
18. A method of identifying a molecule which recognizes and binds an allosteric site on DCMTase comprising:
 - (a) contacting a molecule with DCMTase in the presence of DNA and AdoMet;
 - (b) measuring DCMTase activity, an increase or decrease in DCMTase activity being indicative of a modulator of DCMTase; and
 - (c) determining whether the modulation of DCMTase activity is via binding an allosteric site on DCMTase.
19. The method of claim 18, wherein the modulator is an inhibitor.
20. The method of claim 18, wherein DCMTase activity is measured using a steady-state assay.

FIG.1a.

Synthetic DNA Substrates Mimicking Transcriptional
Cis-Regulatory Elements

GC-box a: 5'-GGGAATTCAAGGGGCGGGCAAGGATCCAG -3'

GC-box b: 5'-CTGGATCCTTGCCCCGCCCCCTTGAATCCCC -3'

GC-box b MET: 5'-CTGGATCCTTGCCC^mCGCCCCTTGAATCCCC -3'

CRE a: 5'-GGGAATTCAAATGACGTC^mCAAAAGGATCCAG -3'

CRE b: 5'-CTGGATCCTTTTGACGTC^mATTGAATCCCC -3'

CRE a MET: 5'-GGGAATTCAAATGA^mCGTCAAAAGGATCCAG -3'

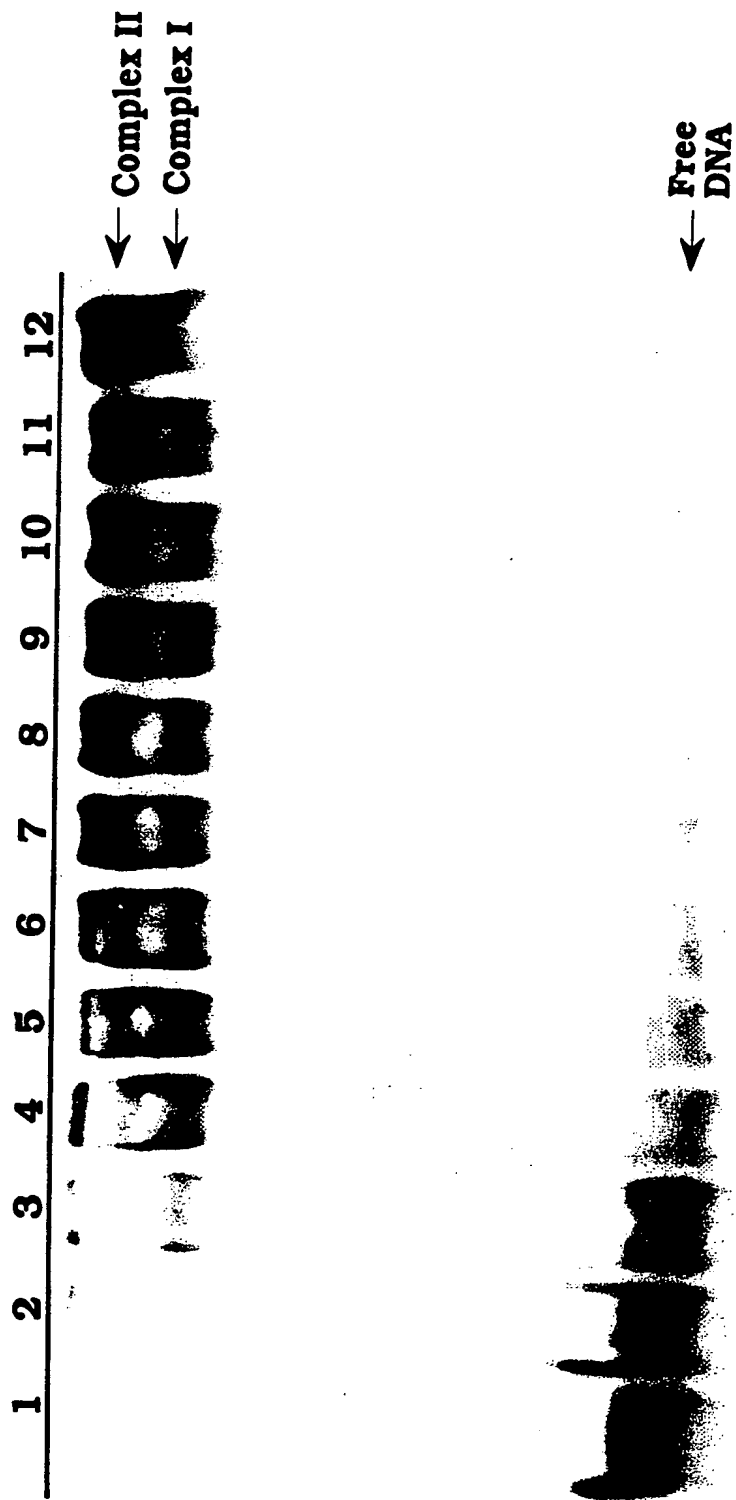
FIG. 1b.

NAME	NUCLEO- TIDES	Sequence	Kii IC50 (nM) (nM)
GC-Box b (SEQ ID NO: 10)	30	5'-CTGGATCCTTGCCCCGCCCTTGAATTCCC-3'	6800
GC-Box bMET (SEQ ID NO: 10)	30	5'-CTGGATCCTTGCCCCmCGCCCCCTTGAATTCCC-3'	20 15
GC Box pMET (SEQ ID NO: 10)	30	5'-CTGGATCCTTGCCCCmCGCCCCCTTGAATTCCC-3'	5
GC-Box cMET (SEQ ID NO: 13)	50	5'- CCTACCCACCCTGGATCCTTGCCCCmCGCCCCCTTGAATTCCCAACCCCTCCAC-3'	30
GC Box dMET (SEQ ID NO: 14)	22	5'-ATCCTTGCCCCmCGCCCCCTTGAAT-3'	50
GC-Box eMET (SEQ ID NO: 15)	14	5TTGCCCCmCGCCCCCTT-3'	150
CRE aMET (SEQ ID NO: 11)	30	5'-GGGAATTCAAATGAmCGTCAAAGGATCCAG-3'	> 300

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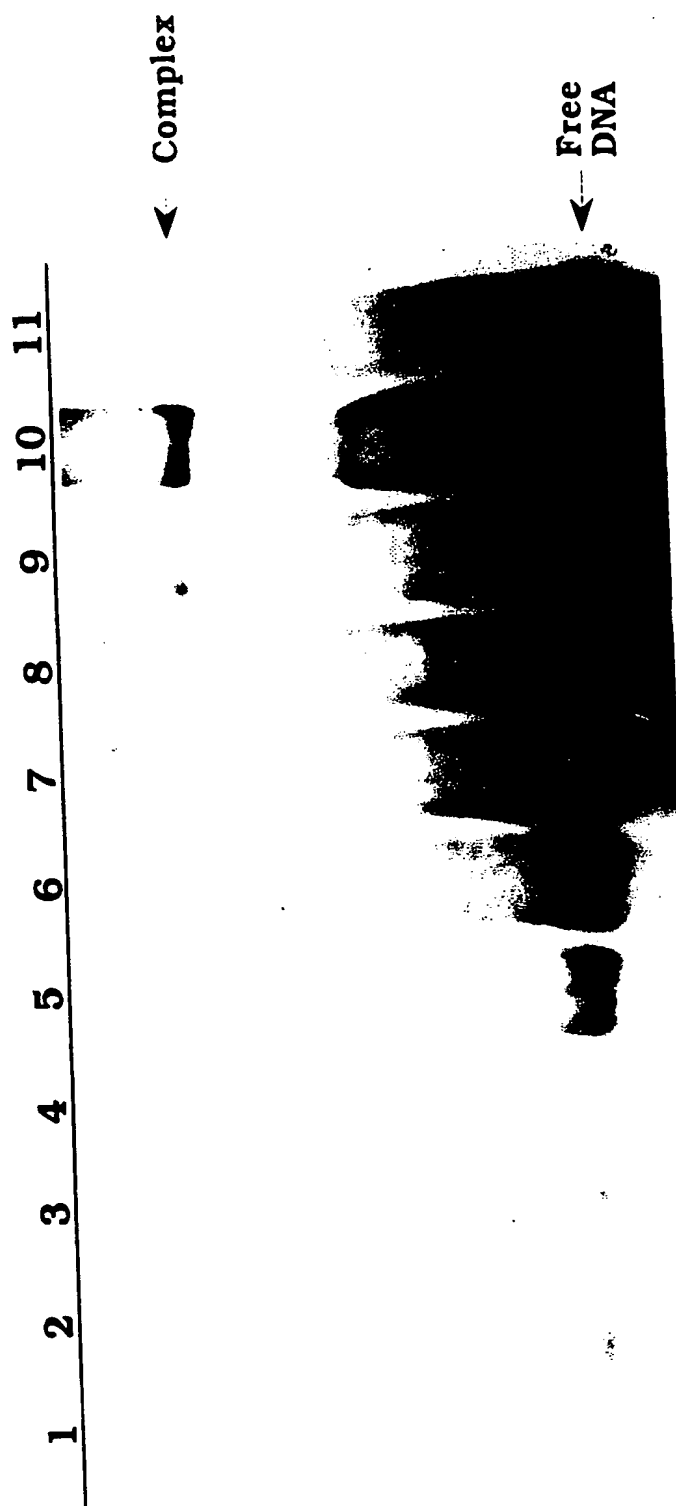
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FIG. 2.



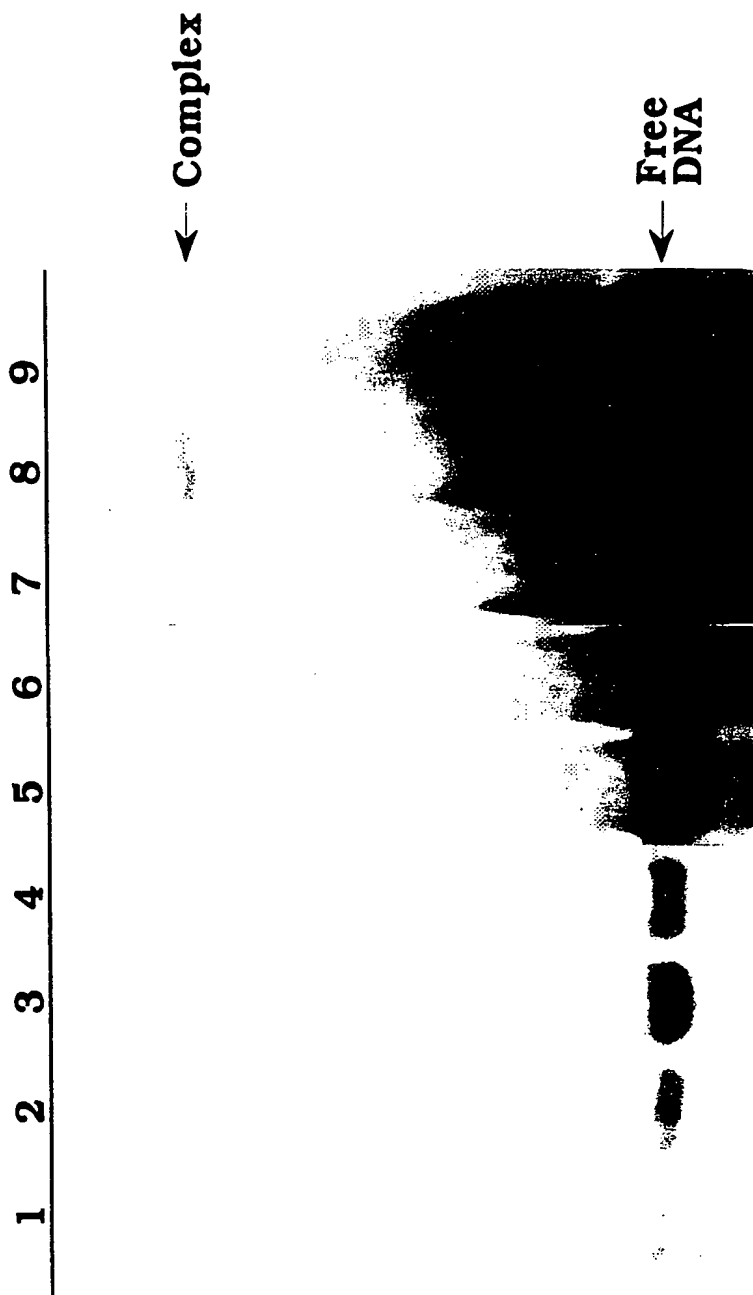
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FIG. 3.



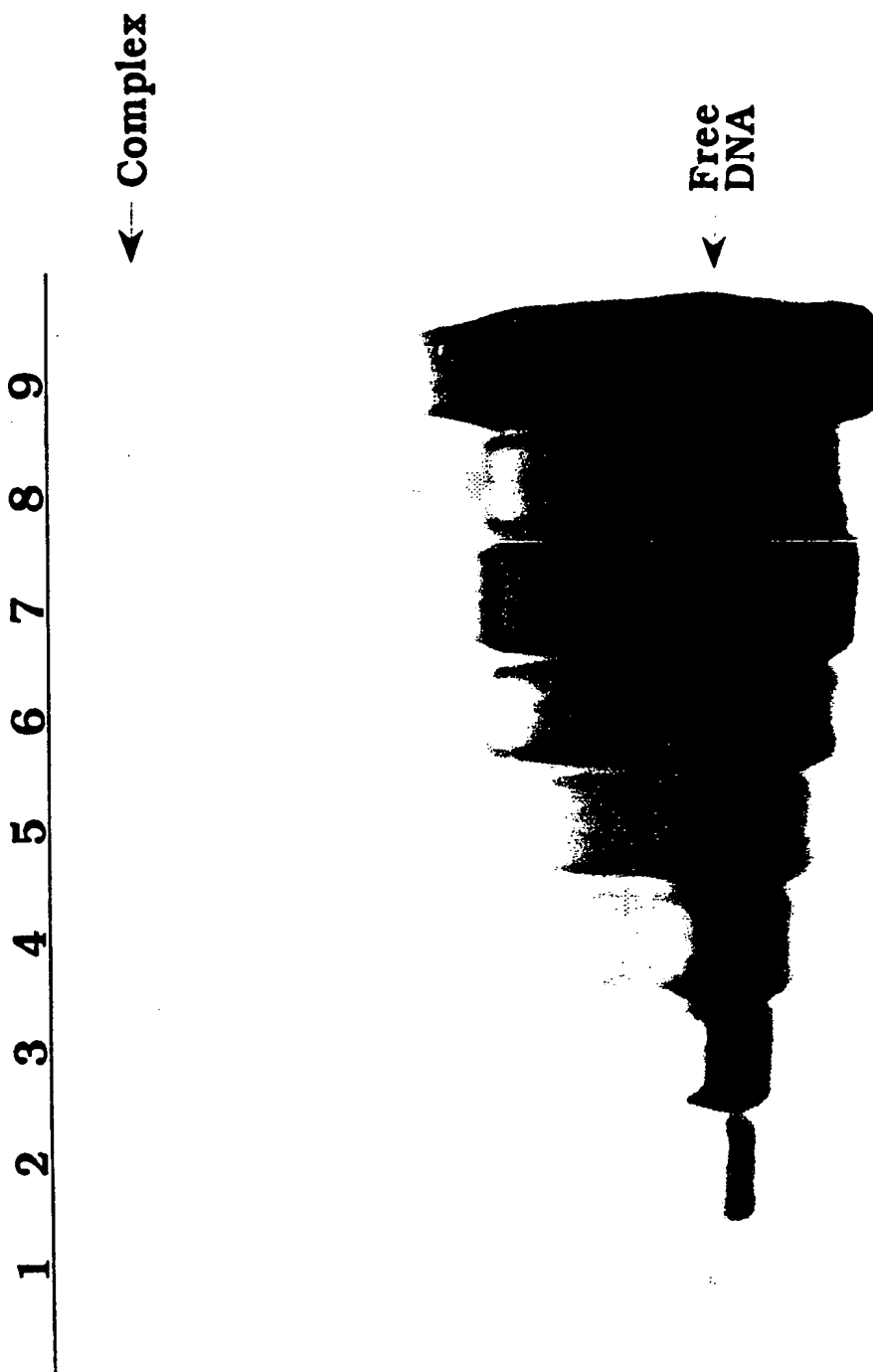
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FIG. 4



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FIG. 5



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FIG. 6.

Primer C

5'-GGGAATTGATCCTAAANNNNNNNNNNCGNNNNNNNNNTTCAAGCTTGTGAATTCCC-3'3'-CCCTTAAGTACCTAGGATTTNNNNNNNNNNGCNCNNNNNNNNNAAAGTTCGAACACTTAAGGG-5'

Primer D

FIG.7a.

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STARTING POPULATION

GTGGGATGGGAACGAGTTGAGGAGGG
AGTGGTATGTATCGATTATACGTTGGG
GGAGGAAGTTTACGTATGGTATGGGG
TGGGAGGGGATTCGAGGTGAGAGTTG
ATAAAGTATTAGCGTAAGAGATGAAG
TGGAGGAGTTTACGGTGTAATTGTTT
GGAGTAGGTAGACGTTAAGTATGATG
GTGGGAAGGGGACGAATTTGAAGGTG
TGGTAATGTATTCGTAATGTAAGGG
TAATAGGGGAGACGTAAATGTAAGGG
GAGTGTAGAAGTCGTAATAGATTTAG
TGAGTAGGAAAGCGAAGAGGTGTTGG

FIG.7b.

GENERATION 1

TAGGTATTGGGGCGGAAGGTGGGTGG
GGGGGTATAATACGGTGTTGGTAGGG
GGGTTGGGGTTTCGTGTGGGGGGTGT
TGTGGGTATGGGCGGTGATAGTGAAG
GGATGATGGGGTCGAGAGTGGTGGTG
TAGTGGGTGGAGCGAGTGGTGGTTGG
AGGGTGGGTGGGCGAGTTGTTGTTG
GTGAGGAGGGAGCGGGAATGGGGGTG
GGGGGTGGGGAGCGGAGGGGGGGTGAG
TGTTGGAGGGGGCGAAGGTGGTTTTG

FIG.7c.

GENERATION 3

GGGGGGGGGGGGGGCGAGGGGTTAGATGG
GGGGGAGGGGTTCGGTGATAGGTAGG
GGGGGGGGGGGTACGTGGGATGGTATG
GTGTAGGGAGTGCGAGGGGGGTGTAA
GGGGGGGGGGTAGCGGTTAGATGGTGG
GGGGTGAGGGGGCGGGGGTTAGTGGG
GAGGGGGGGGTTGCGTAGGGGGGGTGGG
TGTGGAGGTGGGCGGGAAAGGTGATG
GGGGGGATGGGACGGATGGGGGGGGG
GGGGGTGGGGTGCGAGAGAGTTGGGG
GAGGGGTGGAGGCGGAGGTGGGTTGG
GGGGGGGGGGGGCGATAAGGGGTGTG

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FIG. 7d.

G#	GpT	TpG	GENERATION 5	TpG	GpT	G#
11	.	.	TGGGGGGGGG <u>CGGGG</u> GAGTTGA	.	.	7
11			GGGGGGAGGG <u>CGG</u> ATAGTTGTGTG	5
10	GGGTGGGGTGGG <u>CGG</u> TGGGGTGTGGG	9
10			GAGGGGGGAG <u>CGG</u> AGGGGTTGGG	.	.	9
10			GGGGGGGAAGGG <u>CGG</u> TGGGGTTGGGTG	8
10			-GGAGGGGGGG <u>CGG</u> ATGGGGTGGTGG	8
10	GGGTGGGGTGGG <u>CGG</u> TGTGGGTGGGG	8
10	.	.	GGGAGGGGGTGGG <u>CGG</u> TGGGTATGTGG	7
10	.	.	GGGGAGGGTGGGCGGGGTATGGAGTGG	7
10	.	.	GGGGGGGAGTGG <u>CGG</u> TGATGGGTGTG	6
9	.	.	GGGGGGGTGGATCGTGGGGGAGGGG	.		10
9	GGGGTAGGGTGGG <u>CGG</u> GGGGGTATGG	.	.	9
9	.	..	GGGATGGGGGTGGG <u>CGG</u> TATGGGGG	.	.	9

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FIG. 7e.

G#	GpT	TpG	GENERATION 5	TpG	GpT	G#
9	•		GGGAGGGGTAGCGGAGTGTGTGTG	7
9	•		GGGGGTAAGGGCGTAAGAAATGGGGG	.		6
9	••	•	GGGGGGTGGTTCGGTAATGGGGGGT	.	••	7
9	•	•	GGTGGGAGAGGGCGTGGTGTAGGTAG	••	•••	6
9	••	•	GGGGGGGTGTACGAGGTTTGTGTGG	•••	•••	6
9	•	••	TGGTGGAGGGGGCGAAGAGTGTGTG	•••	•••	5
9	•	••	GGGGGTGGGATGCCGGAATAAGGATGG	.		6
9		•	TGAGGGGAGGGCGAATAGATGGTGG	••	.	7
8	•		GGGGGGAGTAAGCGGGGTGTGGTGG	•••	•••	9
8	•	••	TGAAGGGGGGTGCGGGGTGTGGGGG-	••	••	9
8	••	•••	GTGGTGATGGGGCGGGGTGGTAGTGG	••	•••	8
8	•	•	TGGAGGGGTAGGCCGTGGGGGTGATGGG	•••	.	8

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FIG. 7f.

GENERATION 5				
G#	GpT	TpG	GpT	G#
8	8
8	8
8	7
8	6
7	10
7	10
7	9
7	9
7	9
7	8
7	8
7	7

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FIG. 7g.

GENERATION 5				
G#	GpT	TpG	GpT	G#
7	•	••	••	7
7	•••	••	••	7
7	••	••	••	7
7	••	••	••	7
7	••	••	••	6
7	••	••	••	5
6	•	••	••	8
6	••	••	••	6
6	•	•••••	•••••	6
6	•••••	••	•	4
5	••	•	•	10
5	•	•	•	9

FIG.8a.

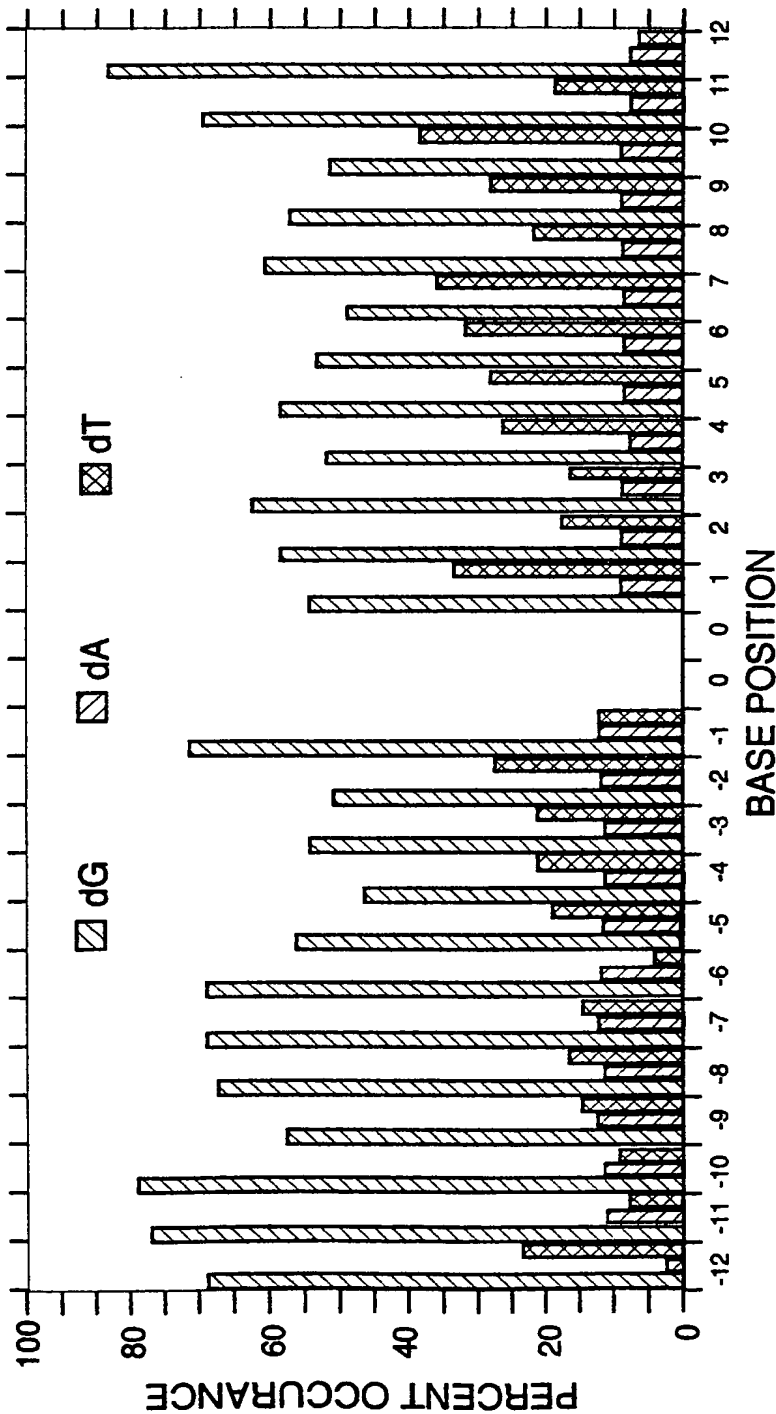


FIG.8b.

%G	73	82	84	61	71	73	73	59	49	57	53	76	0	100	57	61	65	53	61	55	51	63	59	53	73	88
%A	2	10	6	22	10	10	22	20	29	20	18	12	0	0	10	20	18	20	10	12	12	14	12	6	6	6
%T	25	8	10	16	18	16	4	20	22	22	29	12	0	0	33	18	16	27	29	33	37	22	29	41	20	6
%C	0	0	0	0	0	0	0	0	0	0	0	0	100	0	0	0	0	0	0	0	0	0	0	0	0	0

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FIG.9a

DEFINITION Lyt-2.2 gene, T- cell differentiation antigen, 3' UTR.
ACCESSION GB_RO:MMLYT22

TGGGGGGGGGGGCGGGGGGAGTTTGA
| | | | | | | | | | | | | | | | | |
GAACAATGGGGGCGCTGGGGGGGGGGCGGGGGGCTTTAGCTATGTCAGAAATCA
5100 5110 5120 5130 5140

DEFINITION homeo box 2.6 (Hox-2.6) mRNA
ACCESSION GB_RO:MUSHOX26

GGGATGGGGGTGCGGGGGTATGGGGGG
| | | | | | | | | | | | | | | | | |
GGGGAACAGCGAGCCCGAAGGGGTGCGGGGTATGGGAGGGTCCCCGGGCTTGAGC
870 880 890 900 910 920

DEFINITION growth arrest-specific promoter gene, gas-1
ACCESSION GB_RO:MMGAS1PRA

GGTGGTGGTGATCGGGGTTGTGATGG
| | | | | | | | | | | | | | | | | |
TGTCCTTCTGTGGTGTAGAGGTCGTGGTTGTGATGGTGGCTCGGTGTGTGT
2480 2490 2500 2510 2520

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FIG. 9b.

DEFINITION pim-1 proto-oncogene, pim-1 protein kinase, CpG island,
5' UTR region.

ACCESSION GB_RO:MUSPIM1

GAGGGGGGAGCGGAGGGGTTGGG
| | | | | | | | | | | | | | | | | |
GAGGGTGTAGCGCGAGGGGCGGAGCGGAGGGGAGGGCCCTGGTCCCGCGGCC
1500 1510 1520 1530 1540

DEFINITION neuronal dihydropyridine-sensitive L-type calcium
channel alpha-1 subunit mRNA, 3' UTR.

ACCESSION GB_RO:MUSDHPCC

CCCCACCCACAACGCCACCCCCACCC
| | | | | | | | | | | | | | | | | |
TCTTTAATGTCGGTCCACCCCAACCGCCACCCCCCACTGGAGCAAGG
8330 8340 8350 8360 8370 8380

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FIG.9c.

HUMAN SEQUENCES

DEFINITION Huntington's Disease Region, chromosome 4p16.3.
ACCESSION GB_PR:HSL1C2

DEFINITION Human Down Syndrome region of chromosome 21.
ACCESSION GB_HTG:HSAC000002

DEFINITION upstream region of HoxA7 gene, CpG island.
ACCESSION GB_PR:HSHCRDNA

DEFINITION chromosome 22 CpG island DNA
ACCESSION GB_PR:HS303B3

DEFINITION CpG island DNA.
ACCESSION GB_PR:HS167B9F

DEFINITION Y chromosome sex determining region, Yp pseudoautosomal
boundary, PAB1.
ACCESSION GB_PR:HSCAMF3X1

DEFINITION creatine transporter and paralogous genes, pericentomeric
repeats on chromosome 16.
ACCESSION GB_PR:HSU41302

DEFINITION cathepsin D (cat D) gene, exon 5.
ACCESSION GB_PR:HUMCATD3

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FIG.9d.

DEFINITION	argininosuccinate synthetase gene 5' end, CpG island
ACCESSION	GB_PR:HSASG5E
DEFINITION	argininosuccinate synthetase gene 5' end, CpG island
ACCESSION	GB_PR:HUMAS1
DEFINITION	vimentin gene, 5' regulatory region, CpG island.
ACCESSION	GB_PR:HUMVIM
DEFINITION	vimentin gene, exon 1, 5' end CpG island.
ACCESSION	GB_PR:HUMVIM02
DEFINITION	vimentin gene, 5' end, CpG island.
ACCESSION	GB_PR:HUMVIMAA
DEFINITION	vimentin gene, 5' end, CpG island
ACCESSION	GB_PR:HSVIM5RR
DEFINITION	chromosome 22 DNA *SEQUENCING IN PROCESS*, CpG island
ACCESSION	GB_HTG:HS170A2I

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FIG. 10.

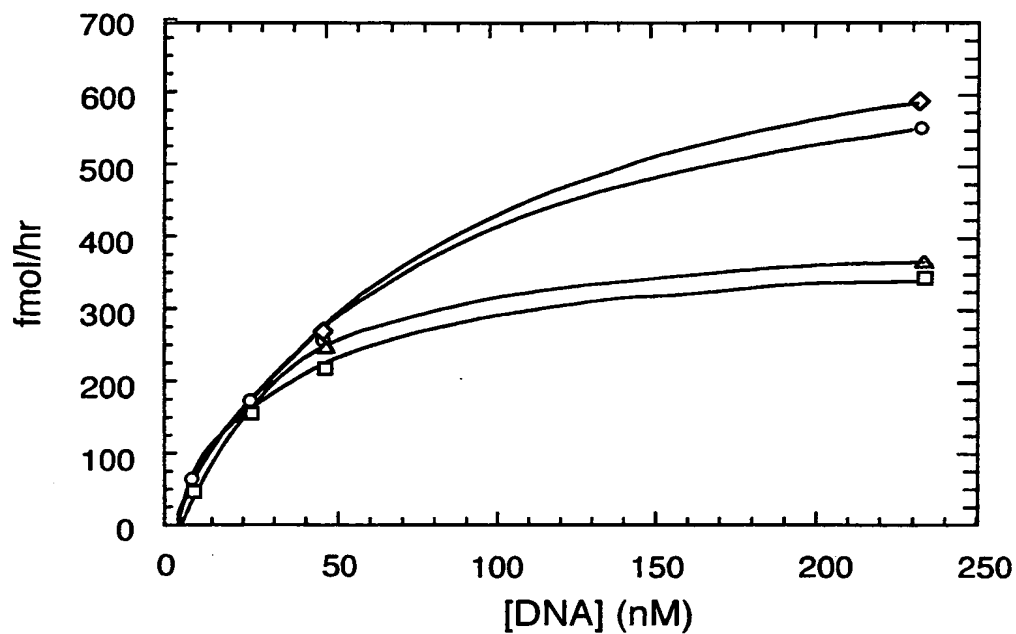
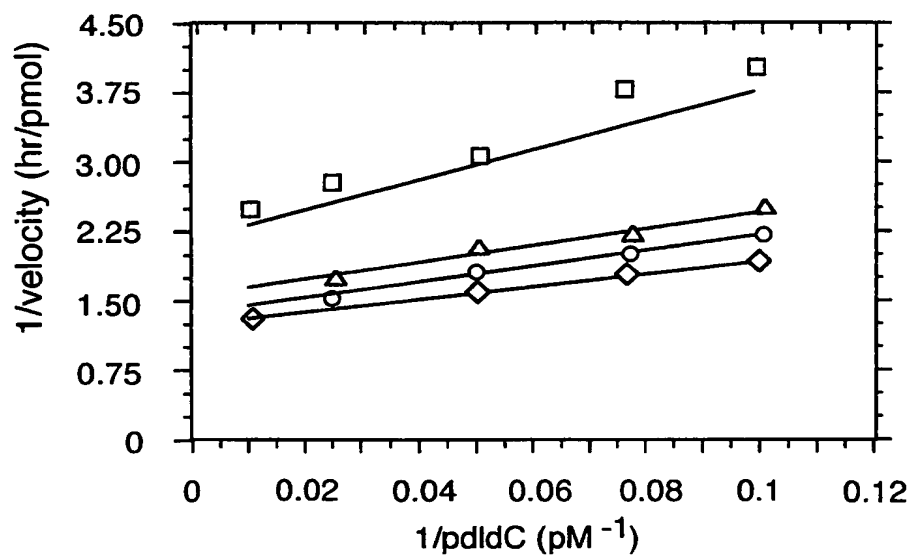
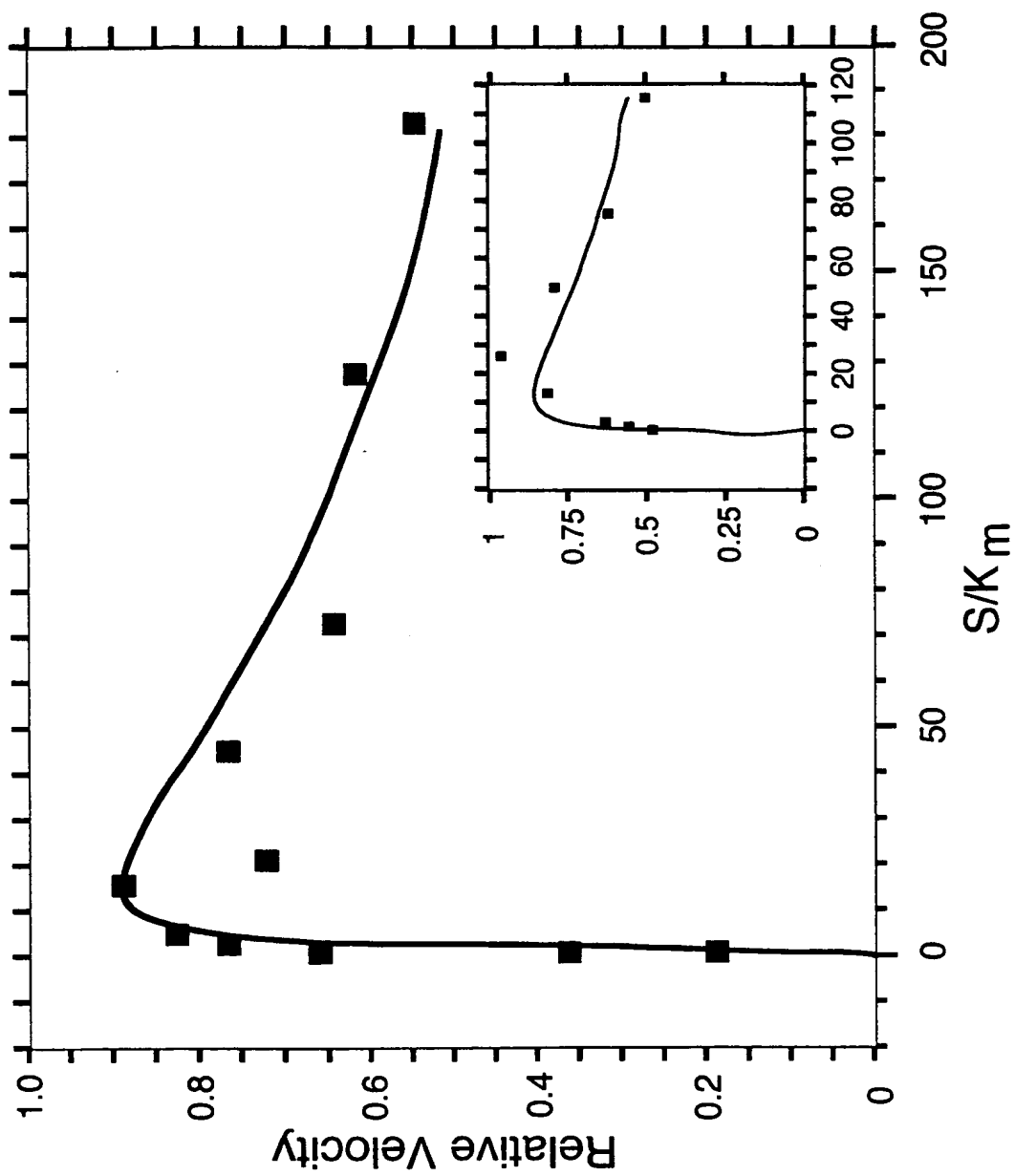


FIG. 13.



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FIG. 11.



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FIG.12a.

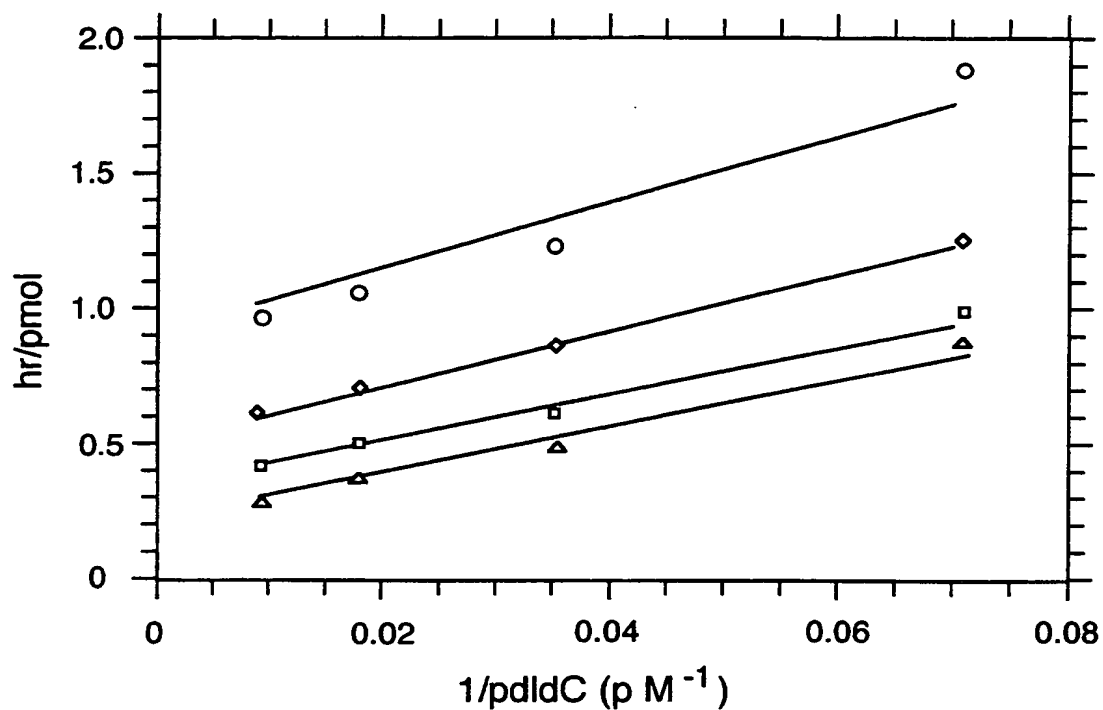
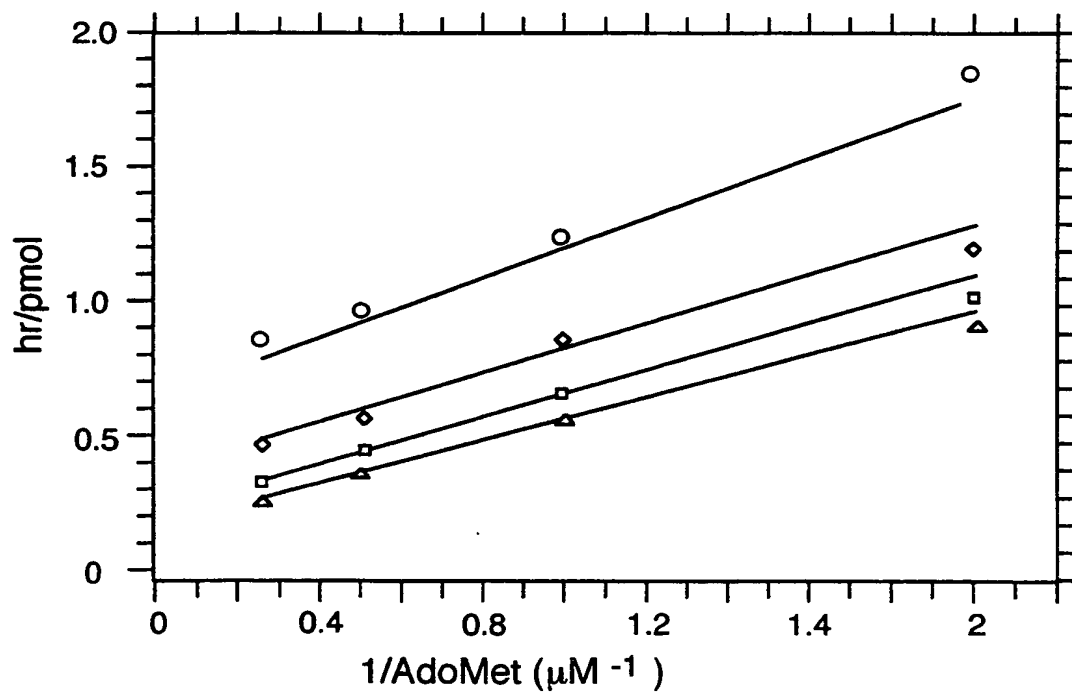


FIG.12b.



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FIG.14.

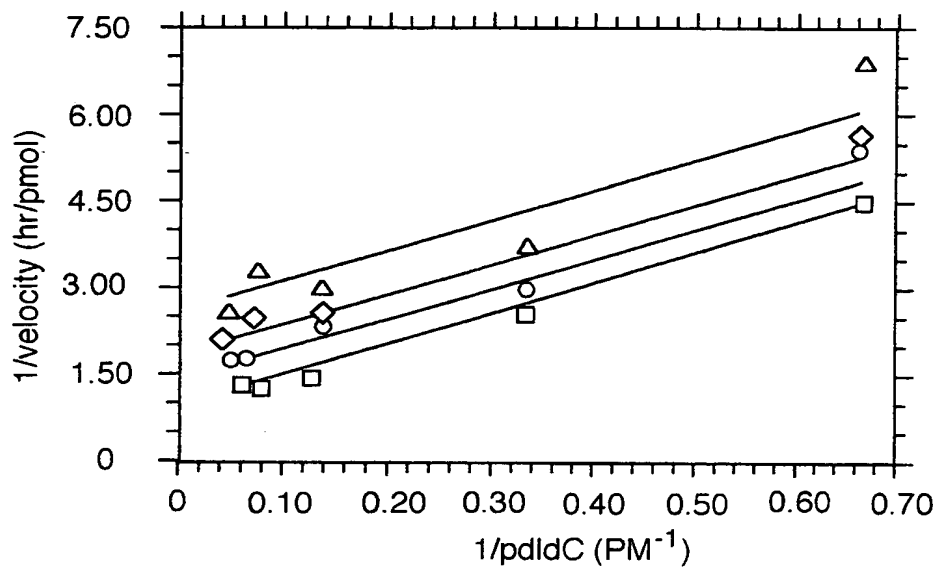
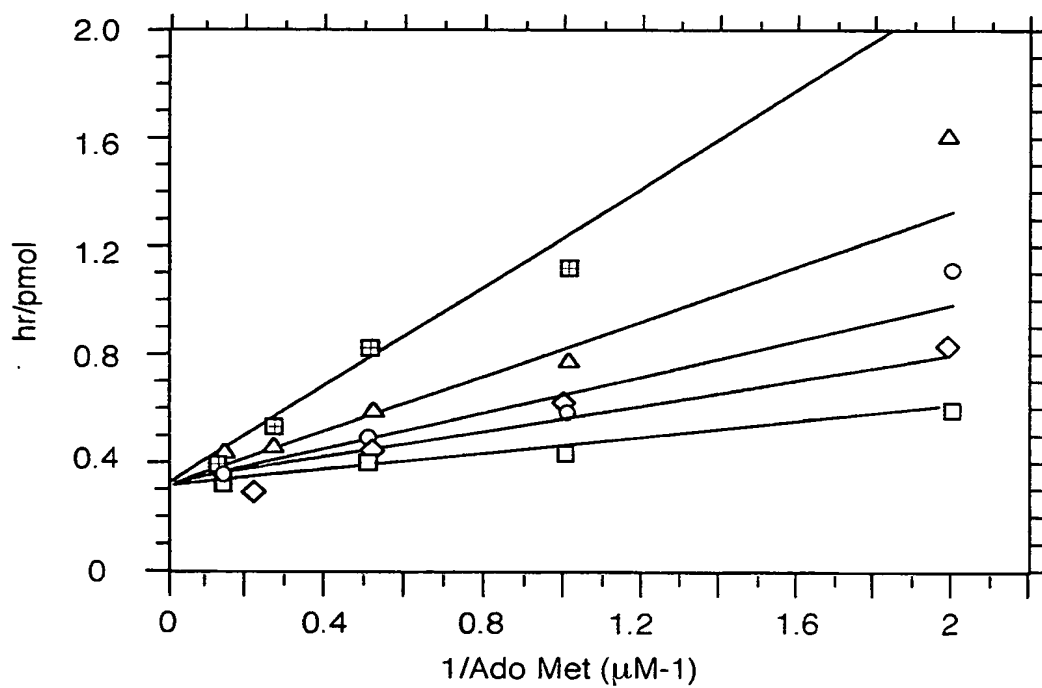
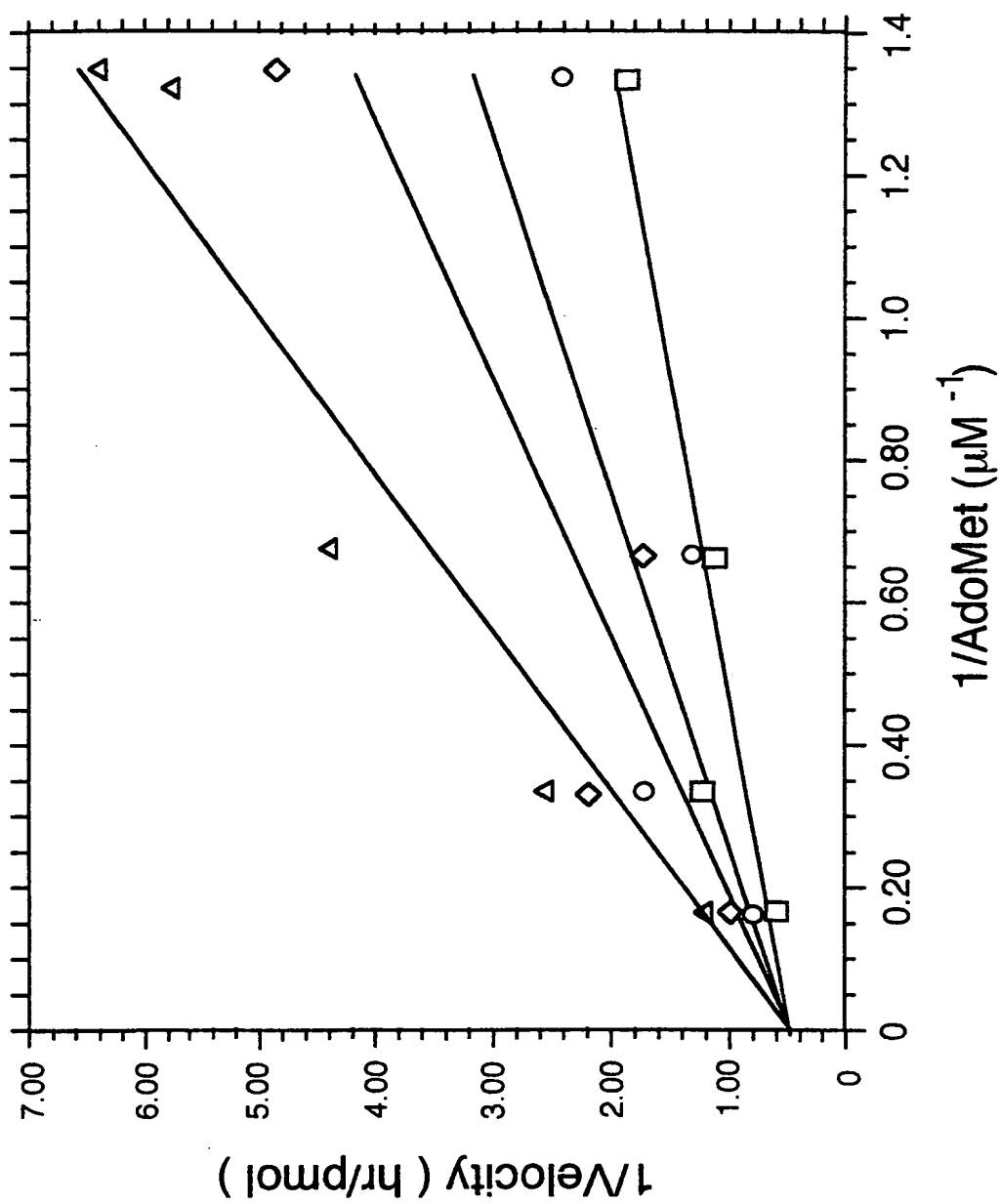


FIG.16.



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FIG. 15.



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FIG. 17a.

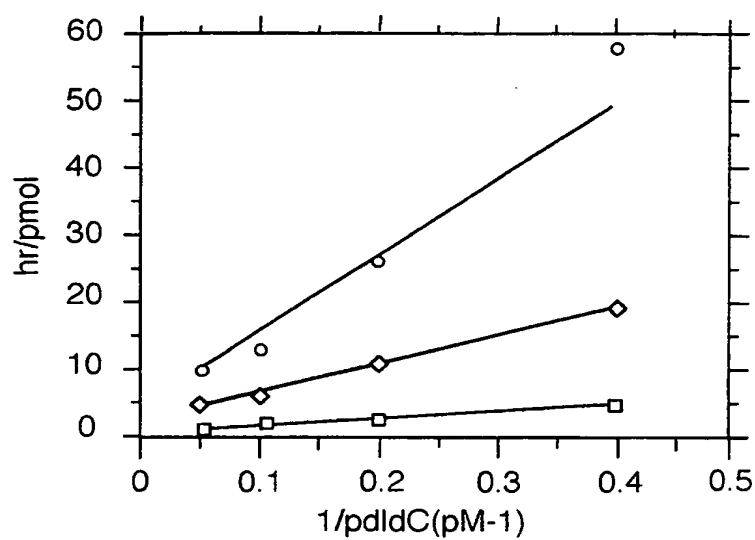


FIG. 17b.

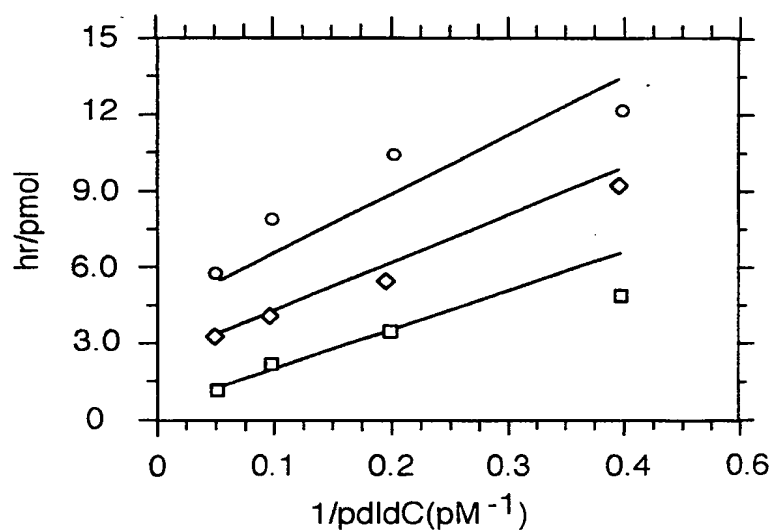
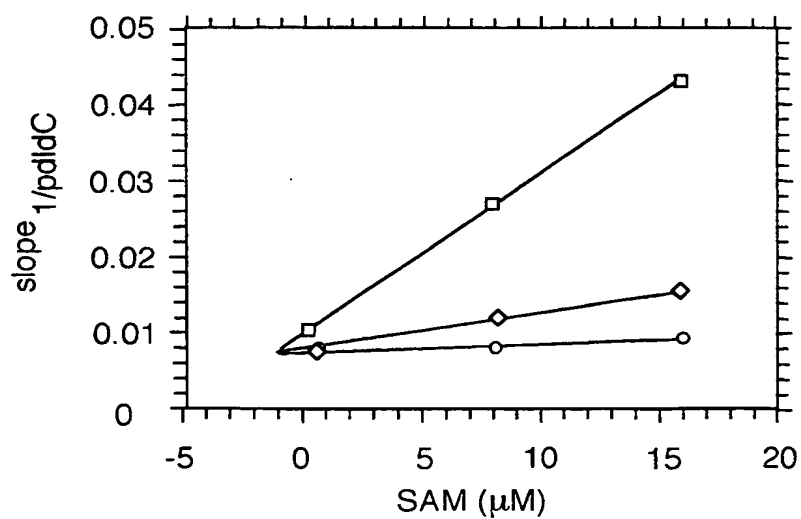


FIG. 17c.



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FIG. 18.

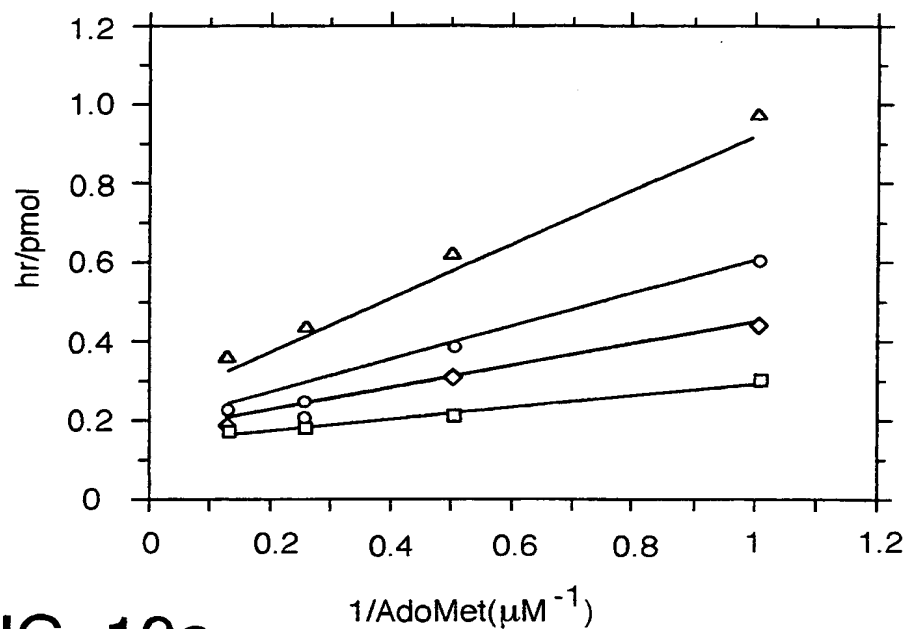


FIG. 19a.

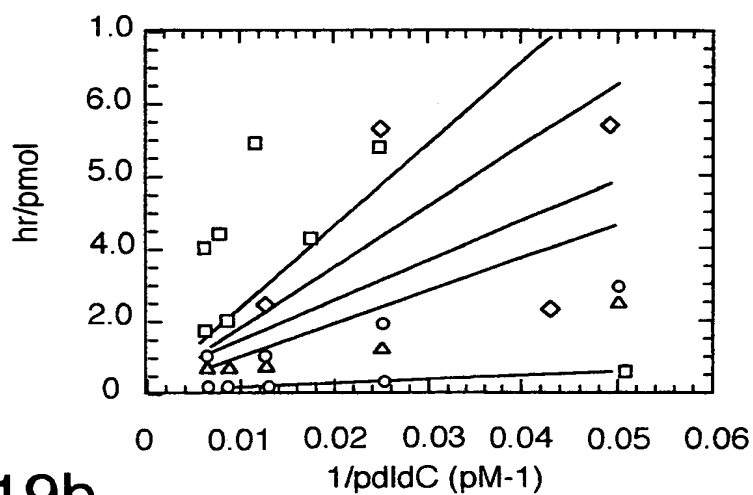
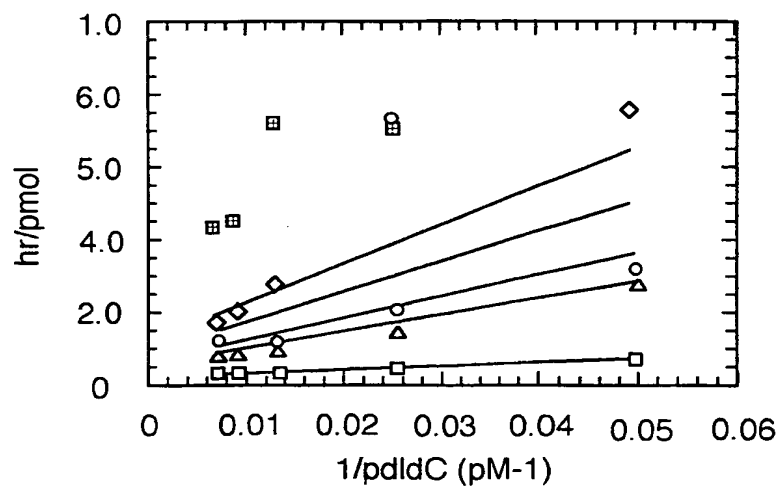


FIG. 19b.



SUBSTITUTE SHEET (RULE 26)

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FIG.20.

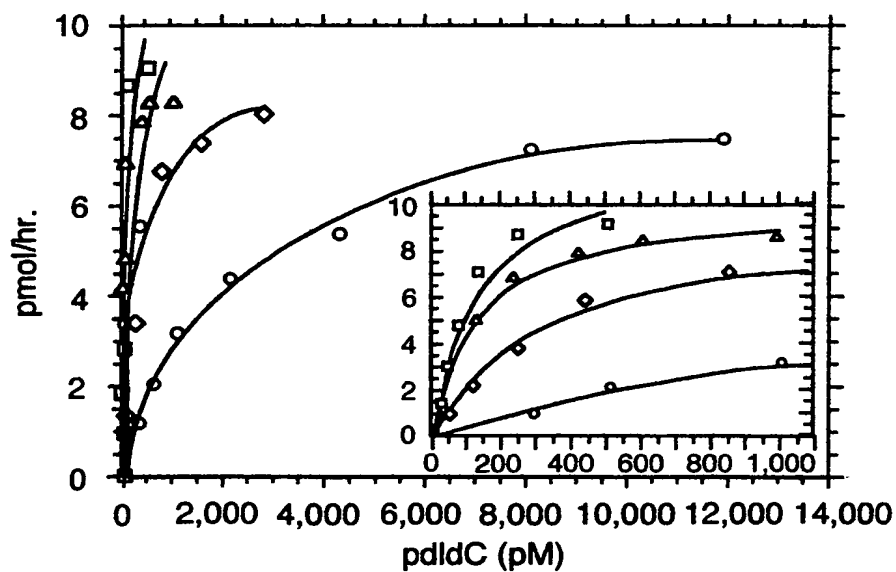


FIG.21.

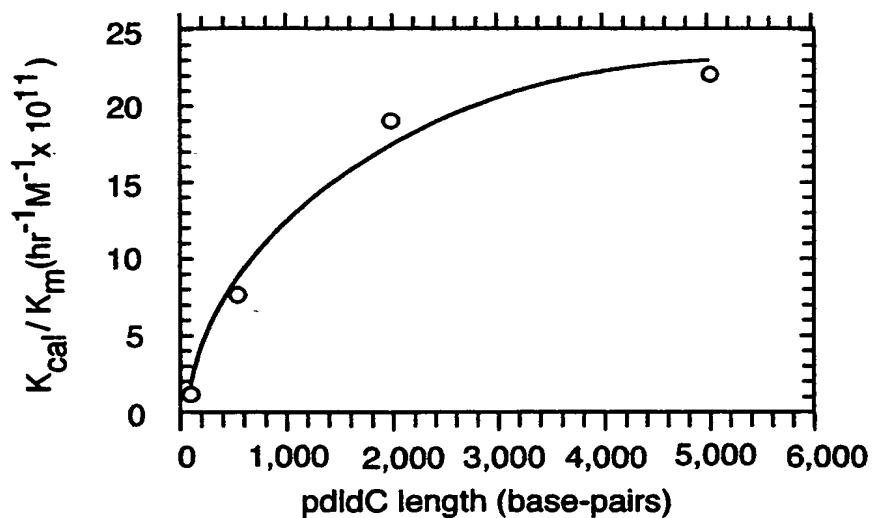
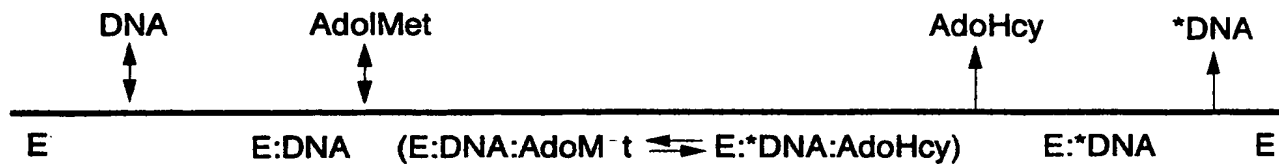


FIG.22.



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FIG.23a.

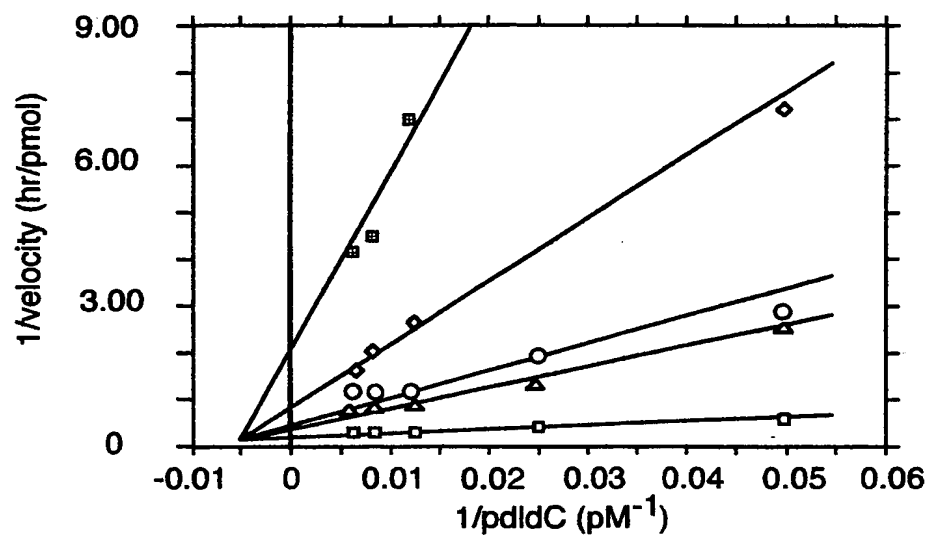


FIG.23b.

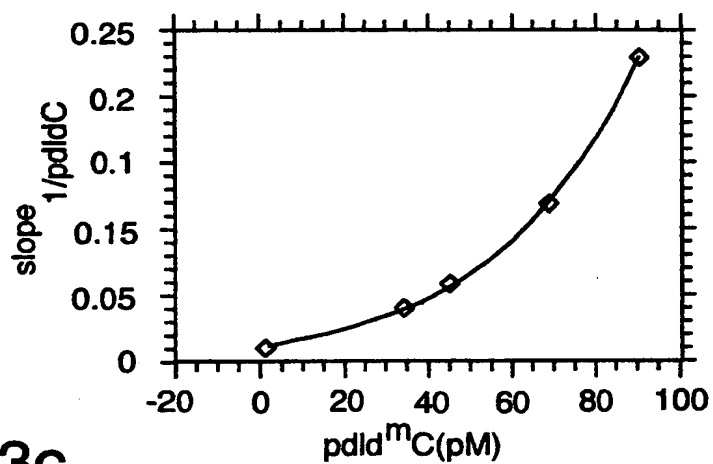


FIG.23c.

